

microtubules which form to pull and separate the newly duplicated chromosome pairs to opposite poles of the cell prior to cell division. In cancer cells which are rapidly dividing, taxane therapy causes the microtubules 5 to accumulate which ultimately prevents further division of the cancer cell. Taxane therapy also affects other cell processes dependant on microtubules such as cell motility, cell shape and intracellular transport. The major adverse side-effects associated with taxane 10 therapy can be classified into cardiac effects, neurotoxicity, haematological toxicity, and hypersensitivity reactions. (See *Exp. Opin. Thera. Patents* (1998) 8(5), hereby incorporated by reference). Specific adverse side-effects include neutropenia, 15 alopecia, bradycardia, cardiac conduction defects, acute hypersensitivity reactions, neuropathy, mucositis, dermatitis, extravascular fluid accumulation, arthralgias, and myalgias. Various treatment regimens have been developed in an effort to minimize the side 20 effects of taxane therapy, but adverse side-effects remain the limiting factor in taxane therapy.

It has been recently discovered *in vitro* that COX-2 expression is elevated in cells treated with taxanes. Elevated levels of COX-2 expression are associated with 25 inflammation and generation of other COX-2 derived prostaglandin side effects. Consequently, when taxane therapy is provided to a patient, the administration of a COX-2 inhibitor is contemplated to reduce the inflammatory and other COX-2 derived prostaglandin side 30 effects associated with taxane therapy.

Taxane derivatives have been found to be useful in treating refractory ovarian carcinoma, urothelial

cancer, breast carcinoma, melanoma, non-small-cell lung carcinoma, gastric, and colon carcinomas, squamous carcinoma of the head and neck, lymphoblastic, myeloblastic leukemia, and carcinoma of the esophagus.

5 Paclitaxel is typically administered in a 15-420 mg/m² dose over a 6 to 24 hour infusion. For renal cell carcinoma, squamous carcinoma of head and neck, carcinoma of esophagus, small and non-small cell lung cancer, and breast cancer, paclitaxel is typically 10 administered as a 250 mg/m² 24 hour infusion every 3 weeks. For refractory ovarian cancer paclitaxel is typically dose escalated starting at 110 mg/m².

15 Docetaxel is typically administered in a 60 - 100 mg/M² i.v. over 1 hour, every three weeks. It should be noted, however, that specific dose regimen depends upon 20 dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient; the route of administration; the renal and hepatic function of the patient; and the particular agents and combination employed.

25 In one embodiment, paclitaxel is used in the present invention in combination with a cyclooxygenase-2 inhibitor and with cisplatin, cyclophosphamide, or doxorubicin for the treatment of breast cancer. In another embodiment paclitaxel is used in combination with a cyclooxygenase-2 inhibitor, cisplatin or carboplatin, and ifosfamide for the treatment of ovarian cancer.

In another embodiment docetaxal is used in the present invention in combination with a cyclooxygenase-2 inhibitor and in combination with cisplatin, cyclophosphamide, or doxorubicin for the treatment of 5 ovary and breast cancer and for patients with locally advanced or metastatic breast cancer who have progressed during anthracycline based therapy.

The following references listed in Table No. 11 below, hereby individually incorporated by reference 10 herein, describe various taxanes and taxane derivatives suitable for use in the present invention, and processes for their manufacture.

Table No. 11. Taxanes and taxane derivatives

EP 694539	EP 683232	EP 639577	EP 627418
EP 604910	EP 797988	EP 727492	EP 767786
EP 767376	US 5886026	US 5880131	US 5879929
US 5871979	US 5869680	US 5871979	US 5854278
US 5840930	US 5840748	US 5827831	US 5824701
US 5821363	US 5821263	US 5811292	US 5808113
US 5808102	US 5807888	US 5780653	US 5773461
US 5770745	US 5767282	US 5763628	US 5760252
US 5760251	US 5756776	US 5750737	US 5744592
US 5739362	US 5728850	US 5728725	US 5723634
US 5721268	US 5717115	US 5716981	US 5714513
US 5710287	US 5705508	US 5703247	US 5703117
US 5700669	US 5693666	US 5688977	US 5684175
US 5683715	US 5679807	US 5677462	US 5675025
US 5670673	US 5654448	US 5654447	US 5646176
US 5637732	US 5637484	US 5635531	US 5631278
US 5629433	US 5622986	US 5618952	US 5616740